DEPARTMENT OF HEALTH AND HUMAN SERVICES — PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Division of Biostatistics (HFM-215)

Statistical Review

FDA NUMBER: 98-1396

TASK TYPE: BLA

SPONSOR: *Elan Pharmaceuticals*

SUBJECT: *Amendments for Product License Application for Neurobloc in the treatment of patients with cervical dystonia*

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BACKGROUND

This current review amends the previous review of the efficacy and safety data from the clinical trials for Neurobloc in the treatment of patients with cervical dystonia (CD). It focuses on the sponsor's responses to the PLA Complete Review (CR) Letter and the safety data from the final report for protocol AN072-352.

Elan submitted this Product License Application for Botulinum Toxin Type B (Neurobloc) on December 22, 1998. The PLA submission included reports for studies AN072-009, 301, 302, 351, and 352. Protocols 301 and 302 were the two pivotal trials for this PLA Application.

Protocol 301 was a multi-center, double-blind, placebo-controlled, single-dose study of the safety and efficacy of a single treatment of Neurobloc in patients with CD. Patients were randomized to receive either placebo or 1 of 2 doses of Neurobloc (5000 U or 10000U). One hundred and nine patients were enrolled into this study. Protocol 302 was a multi-center, double-blind,

placebo-controlled, single-dose study of the safety and efficacy of a single treatment of Neurobloc in patients with CD who have developed resistance to Botulinum Toxin A. Patients were randomized to received either placebo or 10000 U of Neurobloc. Seventy-seven patients were enrolled into this study.

For both protocols (301 & 302), patients were evaluated at Weeks 2, 4, 8, and 16 after dosing and the primary efficacy endpoint was Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The primary efficacy analysis was to compare TWSTRS-Total scores at Week 4 between the placebo and the 10000-U groups using ANCOVA. The independent variables in the model were baseline score, center and treatment group. The mean TWSTRS-Total score at Week 4 was lower among patients treated with Neurobloc compared to the placebo patients. The difference between the two groups in TWSTRS-Total score was statistically significant ($p<0.01$) in both studies. Analyses on the other efficacy endpoints were also consistent with the results from the primary efficacy analysis.

The Agency completed the review of all submissions made related to this Application and found that the information and data submitted were inadequate for final approval action at that time. A CR Letter was sent to the sponsor on October 22, 1999. This review covers the submissions of the sponsor's responses to the PLA CR letter completed on February 16, 2000 and the submission of the final report for AN072-352.

RESPONSES TO THE COMPLETE REVIEW LETTER

Deficiencies regarding the clinical trial reports were summarized on Items 1-21 in the CR letter dated on October 22, 1999. Four individual submissions of the sponsor's responses to the CR letter were sent to the Agency on different times by Elan. The re-submissions include the requested re-analysis of data previously submitted to the application and other clarifying information to the Agency observations.

For the requested antibody testing analysis (Items 7/8), electronic datasets of the ELISA and mouse neutralization assays were also provided with documentation. Based upon the requested analysis of logistic regression on the relationship between the two adverse events (the dry mouth and dysphagia) and the amount of Neurobloc injected (Item 9), the sponsor provided detailed results in the 4th submission. A logistic regression analysis was performed to examine the influence of the amount of toxin injected into each of six muscles (semispinalis capitus, trapezius, sternocleidomastoid, levator scapulae, splenius capitus, and scalene complex) on the incidence of each of two adverse events. Separate analyses were performed for each of four sets of studies and all studies combined. A total of 48 regression models were calculated using the SAS system.

Comment

a. This reviewer has gone through the sponsor's responses to Items 1-21 and found that the responses are adequate.

b. None of the patients in Protocols 301 and 302 was tested antibody positive using mouse neutralization assay. Approximately 10% of the patients were tested positive using ELISA assay and difference between the placebo and Neurobloc groups was not observed.

c. There was a significant POSITIVE association between dose and one of the two adverse events in some logistic models. However, there was also a significant NEGATIVE association between dose and one of the two adverse events in the other logistic models. These results are difficult to be interpreted and should be interpreted with caution since there are a total of 48 p-values from the regression analysis. Nevertheless, a POSITIVE association between dose and dysphagia was observed consistently in the analyses across the studies and all studies combined for the following two injected sites: sternocleidomastoid and scalene complex.

PROTOCOL 352

This was a multi-center, outpatient, open-label, within-patient, dose-escalation study designed to evaluate the safety and tolerability of increasing doses of Neurobloc in patients with CD. The primary objectives of this study were to evaluate the safety and tolerability of Neurobloc in patients with CD by assessing clinical safety parameters, laboratory tests and adverse events; to assess the safety and tolerability of repeat dosing of Neurobloc. This trial had three treatment phases (Phase I, 10000 U; Phase II, 12500 U; and Phase III, 15000 U). Dose escalation for each patient was based upon the investigator's clinical determination of the patient's return to his or her approximate baseline level of CD. One hundred and forty-five patients entered the study and were analyzed. Nine patients received only the 10000-U dose but not the 12500-U or 15000-U doses, 11 patients received both the 10000-U and 12500-U doses but not the 15000-U dose, and 125 received all three doses.

One hundred and thirty-two patients (91%) was reported to have at least one adverse event (AE) in the 10000-U phase, 125 patients (92%) in the 12500-U phase and 96 patients (77%) in the 15000-U phase. Patients in the three treatment phases reported similar types of AEs. The AEs that were reported most frequently were dry mouth, dysphagia and injection site pain. Seventy-nine patients (54%) in the 10000-U phase reported dry mouth, compared with 59 patients (43%) in the 12500-U phase and 42 patients (34%) in the 15000-U phase. Fifty-three patients (37%) in the 10000-U phase had dysphagia, compared with 54 patients (40%) in the 12500-U phase and 26 patients (21%) in the 15000-U phase.

A total of 10 serious adverse events (SAE) were reported by nine patients during the study; three of the SAEs were in the 10000-U phase, four were in the 12500-U phase, and three were in the 15000-U phase. None of these was considered to be related to study drug. One patient died of malignant non-Hodgkin's lymphoma during the study and this case was not considered to be related to study drug.

Effectiveness was also assessed by using TWSTRS, by using the three analog assessments (Patient Global Assessment, Investigator Global Assessment and Patient Analog Pain Assessment) and by determining clinical benefit. The mean TWSTRS-Total score at baseline were 47.2 for the 10000-U phase, 47.0 for the 12500-U phase and 46.9 for the 15000-U phase. Mean improvements from baseline to Week 4 were 9.6 for the 10000-U phase, 10.0 for the 12500-U phase and 10.6 for the 15000-U phase. The mean improvements in TWSTRS-Total scores were greater at Week 4 than Week 8 for each of the dosing phases. Analyses on the other efficacy parameters also show the improvements after receiving Neurobloc.

Comments

a. In this study, the incidence of dry mouth among the dosing phases was highest in patients during the 10000-U phase, while the incidence of dysphagia was highest during the 12500-U phase. These results still hold even if assuming patients who withdrew from the second and the third phases would have had dry mouth and dysphagia if they had received Neurobloc. Under this assumption, seventy-nine patients (54%) in the 10000-U phase reported dry mouth, compared with 68 patients (47%) in the 12500-U phase and 62 patients (43%) in the 15000-U phase. Fifty-three patients (37%) in the 10000-U phase reported dysphagia, compared with 63 patients (43%) in the 12500-U phase and 46 patients (32%) in the 15000-U phase.

b. The results of this study support the safety and tolerability of escalation doses of Neurobloc in patients with CD.

c. The study also shows that patients who received Neurobloc experienced clinical improvements and the improvements in the severity, disability and pain of CD occurred over repeated dosing sessions which are consistent with the efficacy findings from the previous trials.